REMARKS

Claims 21-40 are pending in the application. Claims 21, 22, 30, and 32-40 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 23-29 and 31 are currently being examined on the merits. The Examiner is respectfully reminded that claims 32-34, 39, and 40, directed to methods of using the claimed polynucleotides, are entitled to rejoinder upon allowance of a product claim per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of a product claim, for rejoinder of process claims covering the same scope of products.

Claims 21, 22, 25, 29, and 31 have been amended to further clarify the subject of the claimed invention. No new matter is added by these amendments. Entry of these amendments is respectfully requested.

Restriction Requirement:

The Office Action states that the DNA and protein may be searched and examined together if the claim set is drafted as in Example 17's format and if the DNA and protein are both free over the prior art. The Office Action states that SEQ ID NO:1 was not free over the prior art, as reference polynucleotides AA779652 and AA447814 had identity over portions of polynucleotides encoding SEQ ID NO:1. Applicants respectfully note that the claims are directed to SEQ ID NO:22/101, not to SEQ ID NO:1 or polynucleotides encoding it. No evidence is presented in the current Office Action that either SEQ ID NO:22 or SEQ ID NO:101 are not free of the prior art. Thus Applicants believe that unity of invention should be applied since the claims are linked by a special technical feature (the sequence of SEQ ID NO:22, encoded by SEQ ID NO:101) to form a single inventive concept, and the protein as well as the nucleotide claims should be examined together in this application.

Claim Objections:

Claims 23-29 and 31 are objected to as reciting multiple inventions. The claims have been amended as requested by the Examiner to recite only polynucleotides encoding SEQ ID NO:22.

Claims 23, 24, and 28 are objected to as being dependent upon non-elected claims. As discussed above, Applicants believe that unity of invention should be applied in this case and the polypeptide claims considered along with the polynucleotide claims. However, Applicants will consider amending the claims as requested upon allowance of the polynucleotide claims.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph:

Claims 23-29 and 31 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph for alleged lack of either a specific and substantial asserted utility or a well established utility. **The rejection of claims 23-29 and 31 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art.**

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in humans. The novel polynucleotide codes for a polypeptide (HTMPN-22) demonstrated in the patent specification to be a member of the class of Ring3-related bromodomain proteins, whose biological functions include regulation of transcription and cell growth. As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this brief the Declaration of Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Office Action with respect to the utility of the claimed polynucleotide are without merit.

Applicants note that the instant application is the National Stage of International Application No. PCT/US99/11904, filed May 28, 1999, which claims the benefit under 35 U.S.C. § 119(e) of

provisional application U.S. Ser. No. 60/087,260, filed May 29, 1998 (hereinafter the Tang '260 application). The Tang '260 application contains the same disclosure with respect to the claimed invention as the Tang '590 application. For the sake of convenience, Applicants cite to and discuss the Tang '590 specification below on the understanding that the descriptions in that specification have the May 29, 1998 priority date of the Tang '260 application. Applicants will provide the page and line numbers to indicate the equivalent citations within the specification of the Tang '260 application if the Examiner so requests.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [have appreciated on May 29, 1998] that cDNA microarrays that contained the SEQ ID NO:22-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative and immune disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15.)

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of the biological function of the protein it encodes. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the SEQ ID NO:22-encoding polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Office Action. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '590 priority application, the Tang '260 application, on May 29, 1998 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "specification of the Tang '260 application would have led a person skilled in the art in May, 1998 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of cell proliferative and immune disorders [a] to conclude that a cDNA microarray that contained the SEQ ID NO:22-encoding polynucleotides would be a highly useful tool, and [b] to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:22-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Tang '590 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

skilled in the art would [have appreciated on May 29, 1998] that cDNA microarrays that contained the SEQ ID NO:22-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating cell proliferative and immune disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-May 29, 1998 publications showing the state of the art on May 29, 1998 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include over three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on May 29, 1998 (and for several years prior to May 29, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection with the development of the drug" and how the teachings of the Tang '260 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Tang '260 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:22-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to May 29, 1998" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Tang '260 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Office Action address the fact that, as described on page 55 of the Tang '590 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and

amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cell proliferative and immune disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as cancerous and immortalized cells (see the Tang '590 application at page 88), and expresses a protein that is a member of a class (Ring3-related bromodomain proteins) known to be associated with diseases such as cell proliferative and immune disorders, there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential drug candidate for treating cell proliferative or immune disorders or potential toxin with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-May 29, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Tang '590 priority application, the Tang '260 application, was

filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Tang '260 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized

> toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999) (Reference No. 1, enclosed).

In a pre-May 29, 1998 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added) (Reference No. 2, enclosed).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in

> the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999) (Reference No. 3, enclosed); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No. 4, enclosed).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999) (Reference No. 5, enclosed). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 6, enclosed), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotide can be imputed based on the relationship between the polypeptide it encodes, HTMPN-22, and another polypeptide of unquestioned utility, Ring3. The two polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable probability that the

polypeptide encoded for by the claimed invention has utility similar to Ring3. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

Attached are the results of a BLAST search performed March 2, 1998 (Exhibit A). The BLAST search demonstrated that HTMPN-22 has 57% homology over 548 amino acid residues to mouse Ring3. HTMPN-22 was therefore identified as a Ring3 homolog in column 6 of Table 2 (see page 88 of the specification). Exhibit B shows the results of MOTIFS analysis (see the specification at page 107) performed May 7, 1998 that demonstrates the presence of a bromodomain, a domain found in various transcriptional regulators, from residues A80-N140. This region is shown as a signature sequence in column 5 of Table 2. Thus the specification identified HTMPN-22 as a Ring3-related bromodomain protein.

Articles published before the May 29, 1998 priority date of the instant application demonstrated that Ring3 was a nuclear serine-threonine kinase responsive to a variety of growth factors including IL-1. See Ocstrowski, J., Florio, S.K., Denis, G.V., Suzuki, H., Bomsztyk, K., "Stimulation of p85/RING3 kinase in multiple organs after systemic administration of mitogens into mice," Oncogene 16:1223-1227 (1998) (Reference No. 7, enclosed), page 1223, col. 2. The human RING kinase was known to be very active in leukocytes of patients with acute and chronic leukemias, and "[i]n one leukemic patient in remission the activity of the RING3 kinase in leukocytes returned to normal, suggesting that RING3 kinase may be involved in the pathogenesis of the disease (Ostrowski, page 1223, col. 2). The Ostrowski paper further disclosed that "systemic administration of mitogenic and inflammatory agents into mice stimulates activity of p85/RING3 kinase in a number of organs" (Ostrowski, page 1226, col. 2). The Ostrowski paper concludes that "results of these studies may reflect involvement of p85/RING3 kinase in diseases where abnormal cell proliferation is responsible for the pathological process" which is "consistent with the observation that the activity of this enzyme is very high in leukocytes from patients with acute and chronic leukemias" (Ostrowski, page 1227, col. 1). Thus at the time of filing one of skill in the art would have understood that HTMPN had significant homology to a Ring3, a protein with a known role in cell proliferative and immune disorders.

Furthermore, northern analysis of SEQ ID NO:101 shows its expression predominantly in cDNA libraries associated with cancer, inflammation and the immune response, and fetal development

(specification at page 88). Thus one of skill in the art would have understood at the time of filing that polynucleotides encoding HTMPN-22 would be expected to have utility in the diagnosis of cancers, as described in the specification at, for example, page 53, lines 14-24, or page 54, lines 19-25.

It is undisputed that the polypeptide encoded for by the claimed polynucleotide shares more than 57% sequence identity over 548 amino acid residues with Ring3, a nuclear serine-threonine kinase. In addition, the HTMPN-22 polypeptide contains a bromodomain signature at amino acid residues A80-N140. This is more than enough homology to demonstrate a reasonable probability that the utility of Ring3 can be imputed to the claimed invention (through the polypeptide it encodes). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., "Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA 95:6073-78 (1998) (Reference No. 8, enclosed). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by the claimed polynucleotide is related to Ring3 is, accordingly, very high.

The Patent Office must accept the applicants' demonstration that the homology between the polypeptide encoded for by the claimed invention and Ring3 demonstrates utility by a reasonable probability unless the Patent Office can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Office Action has not provided sufficient evidence or sound scientific reasoning to the contrary.

Instead, the Office Action asserts that "the homology of a peptide is not a reliable indicator of the functional characteristics" (Office Action, page 4). In support of this assertion, the Office Action cites the paper by Scott et al., although no explanation is provided as to how this paper supports the assertion.

The paper by Scott et al. discloses that the protein pendrin was predicted to be a sulfate transporter based upon sequence homology, but later found to be a transporter of chlorine and iodine instead. Applicants respectfully point out that the closest homolog to pendrin, the DRA protein, transports chloride as well as sulfate (Scott et al., page 441, col. 1). Since pendrin's biological function

is believed to be the maintenance of chloride gradients in the inner ear (Scott et al., page 441, col. 2), the homology to DRA is in fact highly related to predictions of pendrin function, if not properly appreciated at the time. This is despite the fact that the degree of homology between pendrin and DRA is only 45%, significantly less than the 57% identity between HTMPN-22 and mouse Ring3. The homology between pendrin and the sulfate transporters was even lower, 29% and 32%. Given the significantly greater degree of homology involved in the current case, one of ordinary skill in the art would be reasonably convinced that HTMPN-22 is indeed a member of the Ring3 related family of bromodomain proteins. In conclusion, the cited reference does not serve to meet the burden of demonstrating that the skilled worker would find it more likely than not that the asserted utility for the claimed protein as a Ring3 related bromodomain protein was not correct. At most, this article stands for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

Furthermore, post-filing art shows that HTMPN-22 has 96% amino acid sequence identity to the short form of human Brd4. As the Office Action mentioned, the gene encoding the long form of BRD4 has 99.2% sequence identity to SEQ I D NO:101 (Office Action, page 11). Applicants note that the Fletcher reference (actually, the French reference, "French, C.A., Miyoshi, I., Aster, J.C., Kubonishi, I., Kroll, T.G., Dal Cin, P., Vargas, S.O., Perez-Atayde, A.R., Fletcher, J.A., *BRD4* bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19)," Am. J. Pathol. 159:1987-1992 (2001) (Reference No. 9, enclosed) made of record in the Office Action is not prior art, as it has a publication date of December, 2001. The French reference discloses that rearrangements of the BRD4 gene are responsible for a particularly aggressive pediatric carcinoma. The French reference further discloses that the short isoform of BRD4 may inhibit BRD4 long isoform function, thus playing a role in the oncogenic mechanism of BRD4 function (French, page 1991, col. 1). An additional postfiling reference (Maruyama, T., Farina, A., Dey, A., Cheong, J., Bermudez, V.P., Tamura, T., Sciortino, S., Shuman, J., Hurwitz, J., Ozato, K., "A mammalian bromodomain protein, Brd4, interacts with replication factor C and inhibits progression to S phase," Mol. Cell. Biol. 22:6509-6520 (2002) (Reference No. 10, enclosed)) discloses that Brd4 is a member of the BET family of bromodomain proteins which includes Ring3, or Brd2 (Maruyama, page 6509) and that Brd4 regulates

cell cycle progression. The French and Maruyama articles thus confirm the identification of HTMPN-22 as a Ring3 related bromodomain protein, and also confirm the association of this sequence with cancers. One of skill in the art would clearly understand that the claimed sequences encoding HTMPN-22, as well as the claimed 90% variants of these sequences, would have utility in the diagnosis of cancer.

D. Objective evidence corroborates the utilities of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. Page et al., in discussing the identification and assignment of candidate targets, states that "rapid identification and assignment of candidate targets and markers represents a huge challenge . . . [t]he process of annotation is similarly aided by the quality and richness of the sequence specific databases that are currently available, both in the public domain and in the private sector (e.g. those

supplied by Incyte Pharmaceuticals)" (Page, M.J., Amess, B., Rohlff, C., Stubberfield, C., Parekh, R., "Proteomics: a major new technology for the drug discovery process," Drug Discov. Today 4:55-62 (1999) (Reference No. 11, enclosed) see page 58, col. 2). As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed polynucleotide and its use of that polynucleotide on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Office Actions's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Office Action attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific, substantial, and credible" utilities (Office Action at pages 5-6). The Office Action is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polynucleotide Is Not Required To Demonstrate Utility

The Office Actions's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific (Office Action, page 4). According to the Office Action, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Office Action would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re*

Cortwright, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Office Action has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Patent Office should have looked first to the benefits it is alleged to provide.

B. Because the uses of polynucleotides encoding HTMPN-22 in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study

properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include utilities in disease diagnosis (pages 51-53), monitoring HTMPN-22 levels during therapeutic intervention (page 50, lines 17-23), genomic mapping (pages 55-56), and in microarrays used to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, page 55, lines 9-15).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel

the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge

of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 23, 24, 26-29, and 31 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description. In particular, the Office Action asserts that the specification does not disclose nucleic acid molecules encoding a polypeptide at least 90% identical to the amino acid sequence of SEQ ID NO:22, or nucleic acids encoding biologically or immunologically active fragments of SEQ ID NO:22. The Office Action asserts that "the skilled artisan cannot envision all the detailed chemical structure of the claimed nucleic acid sequences" (page 7) and the "species specifically disclosed are not representative of the genus because the genus is highly variant" (page 8).

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*

> The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. (Footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

The Specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:22 and SEQ ID NO:101.

SEQ ID NO:22 and SEQ ID NO:101 are specifically disclosed in the application (see, for example, page 11, line 18 and page 12, line 18). Variants of SEQ ID NO:22 having 90% amino acid identity to SEQ ID NO:22 are described, for example, at page 11, lines 30-32. Polynucleotide variants having 90% polynucleotide sequence identity to the polynucleotide encoding SEQ ID NO:22 are described, for example, at page 12, lines 3-6. Polynucleotide variants having 90% polynucleotide sequence identity to SEQ ID NO:101 are described, for example, at page 12, line 32 through page 13, line 2. Incyte clones in which the nucleic acids encoding the human HTMPN-22 were first identified and libraries from which those clones were isolated are described, for example, at page 73 (column 5 of Table 1) and page 97 (Table 4) of the specification. Chemical and structural features of HTMPN-22 are described, for example, at page 79 (Table 2) of the specification. Given SEQ ID NO:22 and SEQ ID NO:101, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID

NO:101 having 90% sequence identity to SEQ ID NO:101 or encoding amino acid sequences having 90% identity to SEQ ID NO:22.

In addition, the specification discloses examples of naturally occurring polynucleotide variants including allelic variants (page 15, lines 22-29), splice variants, species variants, or polymorphic variants, such as single nucleotide polymorphisms (SNPs) (page 23, lines 12-23). The specification discloses how to calculate the % identity between two sequences (see the specification at page 19, line 19 through page 20, line 3), allowing one of skill in the art to determine which naturally occurring sequences are encompassed by the claims. Accordingly, the specification provides an adequate written description of the recited variant polynucleotide sequences.

Regarding the claimed sequences encoding biologically and immunologically active fragments of SEQ ID NO:22, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79). The selection of immunogenic epitopes, such as regions at the C-terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. Note that claim 21(d), as amended herein, recites "an immunologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:22, wherein said immunologically active fragment generates an antibody that specifically binds to SEQ ID NO:22. This amendment was made solely to further clarify the intended subject matter of the claimed invention, and does not further limit the claim scope. Methods of screening antibodies to identify those with desired specificities are disclosed at, for example, page 42, line 30 through page 43, line 5. Furthermore, fragments of polynucleotides encoding SEQ ID NO:22 are disclosed in Column 5 of Table 1, which shows Incyte clones and shotgun sequences which are part of the consensus nucleotide sequence and are useful as fragments in hybridization technologies (page 24, lines 4-6). Thus the specification also provides an adequate written description of the recited polynucleotide sequences encoding biologically and immunologically active fragments. An additional detailed listing of every possible such fragment is not required, and would only result in needlessly cluttering the specification.

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin Cana" or "mammalian insulin Cana," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of functional features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for

isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. The "variant language" of independent claims 21 and 31 recites chemical structure to define the claimed genus:

> 21. An isolated polypeptide selected from the group consisting of . . . b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:22,
>
> 31. An isolated polynucleotide selected from the group consisting of . . . a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:101. . .

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:22 or SEQ ID NO:101. There is no recitation of the functional characteristics of the claimed polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims to nucleic acids. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

B. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference (Reference No. 8) by Brenner et al. Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding RING3 related bromodomain proteins related to the amino acid sequence of SEQ ID NO:22. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as RING3 related bromodomain proteins and which have only 30% identity over at least 150 residues to SEQ ID NO:22. The present claims encompass naturally-occurring polynucleotide variants which have at least about 90% sequence identity to SEQ ID NO:101 or to polynucleotides encoding SEQ ID NO:22. This variation is far less than that of all potential RING3 related bromodomain proteins related to SEQ ID NO:22, i.e., those RING3 related bromodomain proteins having at least 30% identity over at least 150 residues to SEQ ID NO:22.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 29, 1998. Much has happened in the development of recombinant DNA technology in the 21 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the

raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:22 and SEQ ID NO:101, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:22 or SEQ ID NO:101. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids. In addition, the genus of DNA defined by the present claims is not "highly variant," as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and withdrawal of this rejection is therefore requested.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

Claims 23, 24, 26-29, and 31 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate enablement. In particular, the Office Action asserts that the claimed polynucleotide variants and the claimed polynucleotides encoding variant polypeptides and biologically and immunologically active fragments are not enabled. The Office Action asserts that the specification "fails to provide any guidance regarding the changes/modifications contemplated" and that "predicting which

homologues would retain the functions of the protein is well outside the realm of routine" (Office Action, pages 9-10).

Applicants respectfully point out that the claims are directed to polynucleotides, not proteins; thus it is the functionality of the claimed polynucleotides, not the proteins encoded by them, that is relevant. Members of the claimed genus of variants may be useful even if they encode proteins that lack activity. As disclosed in the specification, examples of polynucleotide variants include allelic variants, which result in polypeptides whose structure or function may or may not be altered (page 15, lines 22-29). Further examples of polynucleotide variants include splice variants (which may have additional functional domains or lack domains), species variants, or polymorphic variants, such as single nucleotide polymorphisms (SNPs) (page 23, lines 12-23). The specification discloses how to calculate the % identity between two sequences (see the specification at page 19, line 19 through page 20, line 3), allowing one of skill in the art to determine which naturally occurring sequences are encompassed by the claims.

The specification also discloses how to use the claimed polynucleotide variants. For example, variant sequences having at least 50% sequence identity to HTMPN-22 encoding sequences can be used as probes to detect related sequences (page 50, line 32 through page 51, line 1) including HTMPN-22 variants that may be associated with disease states, such as the diseases listed in the specification at p. 36, lines 4-13). See the specification at, for example, pages 50-54 for disclosure of how to use the claimed sequences in diagnostic assays. SNPs may be used to identify particular human populations, or to identify propensities for disease states (page 23, lines 23-25). The variant polynucleotides could also be used in microarrays to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, page 55, lines 9-15). Thus one of ordinary skill in the art would know how to used the claimed variants without any undue experimentation.

Regarding the claimed biologically active fragments, the specification discloses a specific signature sequence, corresponding to a bromodomain, at residues A80-N140 (specification, page 79). The Office Action does not explain why the claimed immunologically active fragments are not enabled. Applicants respectfully note that the selection of immunogenic epitopes, such as regions at the C-

terminus or hydrophilic regions, is described in the specification at page 70, lines 2-7. Note that claim 21(d), as amended herein, recites "an immunologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:22, wherein said immunologically active fragment generates an antibody that specifically binds to SEQ ID NO:22. This amendment was made solely to further clarify the intended subject matter of the claimed invention, and does not further limit the claim scope. Methods of sceening antibodies to identify those with desired specificities are disclosed at, for example, page 42, line 30 through page 43, line 5. Thus one of skill in the art would have ample guidance in making the claimed polynucleotides encoding biologically and immunologically active fragments.

The biologically active fragments have utility based upon their activity. For example, a bromodomain has utility as a chromatin binding domain (see the French reference, page 1991, col. 1). The immunologically active fragments can be used to generate antibodies, which are useful in the diagnostic methods described in the specification at, for example, page 49, line 29 through page 50, line 16, or in the drug screening methods describes in the specification at page 57, lines 2-5. In addition, the use of catalytic or immunogenic fragments in drug screening is disclosed in the specification at page 56, lines 20-25. Thus one of skill in the art would clearly understand how to use the claimed polynucleotides encoding biologically and immunologically active fragments.

For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: June 24, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims **21, 22, 25, 29, and 31** have been amended as follows:

21. An isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22,

c) a biologically active fragment of a polypeptide having [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22, and

d) an [immunogenic] immunologically active fragment of a polypeptide having [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22, wherein said immunologically active fragment generates an antibody that specifically binds to SEQ ID NO:22.

22. An isolated polypeptide of claim 21 comprising [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22.

25. An isolated polynucleotide of claim 24 comprising [a] the polynucleotide [sequence selected from the group consisting of SEQ ID NO:80-158] of SEQ ID NO:101.

29. A method of claim 28, wherein the polypeptide comprises [an] the amino acid sequence [selected from the group consisting of SEQ ID NO:1-79] of SEQ ID NO:22.

31. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising [a] the polynucleotide sequence [sequence selected from the group consisting of SEQ ID NO:80-158] of SEQ ID NO:101.

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to [a] the polynucleotide sequence [sequence selected from the group consisting of SEQ ID NO:80-158] of SEQ ID NO:101,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).